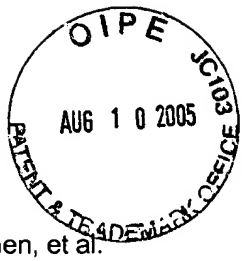
FORM PTO-1083



Docket No.: 300.1023
Date: August 8, 2005

IFW

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COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, VA 22313-1450

In re application of: Chih-Ming Chen, et al.
Serial No.: 09/726,193
Filed: November 29, 2000
For: **CONTROLLED RELEASE METFORMIN FORMULATIONS**

S i r:

Transmitted herewith is an **Appellants Brief on Appeal (in tripilcate) under 37 C.F.R. §1.192** in the above-identified application.

[ ] Small entity status under 37 C.F.R. 1.9 and 1.27 has been previously established.
[ ] Applicants assert small entity status under 37 C.F.R. 1.9 and 1.27.
[X] No fee for additional claims is required.
[ ] A filing fee for additional claims calculated as shown below, is required:

	(Col. 1) REMAINING AFTER AMENDMENT	(Col. 2) HIGHEST PREVIOUSLY PAID FOR	PRESENT EXTRA
TOTAL CLAIMS	* Minus**	=	0
INDEP. CLAIMS	* Minus***	=	0
[ ] FIRST PRESENTATION OF MULTIPLE DEP. CLAIM			

SMALL ENTITY RATE	FEE	OR	LARGE ENTITY RATE	FEE
x $ 9	$		x $ 18	$
x $ 40	$		x $ 80	$
+ $135	$		+ $270	$
TOTAL:	$	OR	TOTAL:	$

[X] Also transmitted herewith are:
[X] Petition for two (2) month extension under 37 C.F.R. 1.136
[] Other:

[X] Check(s) in the amount **$950.00** of is/are attached to cover:
[ ] Filing fee for additional claims under 37 C.F.R. 1.16
[X] Petition for two (2) month extension under 37 C.F.R. 1.136 ($450.00)
[X] Other: Appeal Brief Fee ($500.00)

[X] The Commissioner is hereby authorized to charge payment of the following fees associated with this communication or credit any overpayment to Deposit Account No. 50-0552.

[X] Any filing fee under 37 C.F.R. 1.16 for the presentation of additional claims which are not paid by check submitted herewith.
[X] Any patent application processing fees under 37 C.F.R. 1.17.
[X] Any petition fees for extension under 37 C.F.R. 1.136, and it is hereby requested that this be a petition for an automatic extension of time under 37 CFR 1.136.

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I hereby certify that this correspondence and/or documents referred to as attached therein and/or fee are being deposited with sufficient postage to the United States Postal Service as "first class mail" in an envelope addressed to "Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" on August 8, 2005.

DAVIDSON, DAVIDSON & KAPPEL, LLC

BY:

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.:	09/726,193
Applicant:	Chih-Ming CHEN, et al.
Filed:	November 29, 2000
TC/A.U.	1615
Examiner:	B. Fubara
For:	**CONTROLLED RELEASE METFORMIN FORMULATIONS**
Docket No.:	300.1023
Customer No.:	23280

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

August 8, 2005

APPELLANTS BRIEF ON APPEAL UNDER 37 C.F.R. §1.192

Sir:

Appellants submit this brief for the consideration of the Board of Patent Appeals and Interferences in support of their appeal of the Final Rejection dated October 6, 2004 and the Advisory Action dated February 22, 2005 in the above-identified application. A Notice of Appeal was filed on April 6, 2005, and an Amendment under 37 C.F.R. §1.116 was filed on January 6, 2005. An original and two copies of this brief are submitted herewith. The statutory fee of $500.00 is paid concurrently herewith.

I. REAL PARTY IN INTEREST

The real party in interest is Andrx Labs LLC, a U.S. company having a place of business at 4955 Orange Drive, Davie, FL 33314, USA, assignee of the entire right, title, and interest in the above-identified patent application. The invention was assigned by the inventors Xiu Xiu Cheng, Chih-Ming Chen, Steve Jan, and Joseph Chou to Andrx Corporation. The assignment from the inventors to Andrx Corporation was recorded on May 22, 1998 at reel 009218, frame

0919. The invention was then assigned from Andrx Corporation to Andrx Labs LLC. The assignment from Andrx Corporation to Andrx Labs LLC was recorded on February 25, 2003 at reel 013788, frame 0187.

II. RELATED APPEALS AND INTERFERENCES

Appellants and their legal representatives and assignee are not aware of any appeal or interference that directly affects, will be directly affected by, or will have a bearing on the decision in this appeal.

III. STATUS OF CLAIMS

Claims 1, 4, 6, 8-20, 24-33 and 35-39 are pending in this application. No claims have been allowed, all claims being subject to a final rejection dated October 6, 2004, as narrowed by an Advisory Action dated February 22, 2005, and it is from this final rejection (and Advisory Action) that this Appeal is taken. Claims 1, 4, 6, 8-20, 24-33 and 35-39 remain in the application and are appealed. A copy of these appealed claims is attached hereto as an Appendix.

IV. STATUS OF AMENDMENTS

In the Amendment under 37 C.F.R. §1.116 filed January 6, 2005, claims 1, 6, 8-9, 12, 15, 18, 24, 27, 31, 33, and 35 were amended. In the Advisory Action dated February 22, 2005, the Examiner indicated that for purposes of appeal, the amendment to the claims filed January 6, 2005 will be entered.

V. SUMMARY OF INVENTION

The presently claimed invention is directed to a sustained release pharmaceutical formulation that includes metformin or a pharmaceutically acceptable salt thereof and a sustained release material which provides specific pharmacokinetic parameters after administration to a human patient, such as, e.g., providing an AUC (area under the concentration-time curve) which is increased by the presence of food as compared with administration in the fasting state and/or which do not exhibit a decrease in the bioavailability of metformin if taken with food.

The presently claimed invention is also directed to a method of treating diabetes in humans with an intact sustained release oral dosage form that includes metformin or a pharmaceutically acceptable salt thereof and a sustained release material, which does not exhibit a decrease in the bioavailability of metformin when administered in the presence food or which increases the bioavailability of metformin relative to administration in the fasting state.

In the following arguments, Appellants contrast this invention to the only remaining prior art reference cited by the Examiner, which, to the extent that it teaches a sustained release pharmaceutical formulation including metformin or a pharmaceutically acceptable salt thereof and a sustained release material at all, fails to teach a sustained release pharmaceutical formulation which provides the specific pharmacokinetic parameters provided by the formulations of the present invention and fails to teach swallowing an intact sustained release oral dosage form containing metformin or a pharmaceutically acceptable salt thereof which provides the specific pharmacokinetic parameters provided by the formulations of the present invention.

VI. ISSUES

The following issues are presented for appeal:

(1) Whether claims 1, 4, 6, 8-20 and 24-32 are unpatentable under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,055,306 to Barry et al.

(2) Whether claims 33 and 35-39 are unpatentable under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 5,055,306 to Barry et al.

VII. GROUPING OF CLAIMS

The Examiner has rejected claims 1, 4, 6, 8-20, 24-33 and 35-39 as a single group. However, Appellants believe that claims 1, 4, 6, 8-20, 24-33 and 35-39 may be divided into two

(2) groups for appeal. As argued below, Appellants assert that these groups of claims are separately patentable, and the claims of each group stand or fall together.

Group I includes claims 1, 4, 6, 8-20, 24-29, and 30-32.
Group II includes claims 33 and 35-39.

Appellants believe that these grouping of claims are separately patentable as Group I of the claims is directed towards metformin formulations having certain *in-vivo* characteristics which are obtained from administration of the metformin formulations to humans. The claims of Group II are directed to methods of treatment with the disclosed dosage forms.

Appellants submit that the metformin formulations of Group I can be used to practice other and materially different methods than those methods of Group II. For example the methods in the claims of Group II recite swallowing the solid oral sustained release dosage forms intact, whereas the metformin formulations in the claims in Group I are not required to be swallowed intact.

Thus Appellents believe that these two groups of claims are separately patentable.

VIII. ARGUMENT

A. 35 U.S.C. §102 Rejection of Group I (Claims 1, 4, 6, 8-20, 24-29 and 30-32) Based Upon U.S. Patent No. 5,055,306 to Barry et al.

Independent claim 1 is directed to a sustained release pharmaceutical formulation comprising (i) an active agent consisting of metformin or a pharmaceutically acceptable salt thereof, and (ii) a sustained release material, wherein the formulation provides therapeutic plasma levels of metformin to a human patient over a 24 hour period after administration to the patient; and the formulation providing an AUC which is increased by the presence of food as

compared with administration in the fasting state.

Similar to claim 1, independent claims 6, 8, 9, 12, 15, 18, 24, and 27 are also directed to sustained release formulations including metfomin or a pharmaceutically acceptable salt thereof which provide "an AUC which is increased by the presence of food as compared with administration in the fasting state." Claims 6, 8, 9, 12, 15, 18, 24, and 27 differ from claim 1 in that they recite different pharmacokinetic parameters as follows:

Claim 6 recites the formulation providing a T_{max} of the metformin which occurs at a time from about 8 hours to about 12 hours after administration to a human patient;

Claim 8 recites the formulation providing a peak of a mean plasma concentration/time curve of metformin at a time from about 4 hours to about 10 hours after administration;

Claim 9 recites the formulation providing a peak plasma concentration (C_{max}) of metformin from about 52.8% to about 75.1% of the C_{max} provided by an equivalent dose of metformin in an immediate release reference formulation;

Claim 12 recites the formulation providing a T_{max} of metformin from about 182% to about 200% of the T_{max} provided by an equivalent dose of metformin in an immediate release reference formulation;

Claim 15 recites the formulation providing a T_{max} of metformin from about 173% to about 215% of the T_{max} provided by an equivalent dose of metformin in an immediate release reference formulation;

Claim 18 recites the formulation providing a width at 50% of the height of a mean plasma concentration/time curve from about 6 hours to about 12 hours; and

Claim 24 and 27 recite the formulation exhibiting the particularly claimed dissolution profiles when tested in a United States Pharmacopeia (USP) type 2 apparatus at 75 rpm in 900 ml of simulated intestinal fluid (pH 7.5 phosphate buffer) and at 37° C.

Independent claim 31 is directed to a sustained release once a day oral solid dosage form of metformin, comprising (i) an active agent consisting of an effective amount of metformin or a pharmaceutically acceptable salt thereof and one or more materials controlling the release of

metformin from the dosage form such that the dosage form, when orally administered on a once a day basis to a human in the presence of food, therapeutic levels of the metformin are attained in said human for 12 to 24 hours, and the dosage form does not exhibit a decrease in the bioavailability of metformin if taken with food.

1. The Examiner's rejection

The first issue presented is whether claims 1, 4, 6, 8-20 and 24-32 are unpatentable under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,055,306 to Barry et al. (hereinafter "the Barry reference). In the Final Office Action, the Examiner stated the following:

> Examiner evaluated the functional language recited in the claims and found that the function of the instant metformin formulation is inherent to the metformin formulation of the prior art and applicants provided no demonstration to show that the metformin formulation of the prior art would not possess the recited function/property/characteristic of the instant metformin formulation. And in the Swinehart case referred to by applicants, it is respectfully noted that the opinion reads, 'mere recitation of newly discovered function or property, inherently possessed by things in prior art, does not cause claim[s] drawn to those things to distinguish over prior art; additionally, where [the] Patent Office has reason to believe that functional limitations asserted to be critical for establishing novelty in claimed subject matter may, in fact, be an inherent characteristic of prior art, it possesses authority to require applicant to prove that subject matter shown to be in prior art does not possess characteristics relied on.' Applicants provide no [proof] to show differences between the claimed metformin formulation and the disclosed metformin formulation.
>
> In summary, it appear that applicants' metformin formulation differs from the disclosed metformin formulation and applicants have not yet claimed the difference, provided the difference or claimed the metformin formulation that is applicants' invention. The metformin formulation claimed by applicants reads on the metformin formulation of the prior art. And function or property or characteristic inherent to the broad metformin formulation does not distinguish the claimed metformin formulation from the prior art. Applicants are respectfully encouraged to provide any structural and/or compositional differences between the claimed and disclosed and also provide [proof] that the formulations of the prior art differ [from] the instant broad metformin formulation.

Final Office Action of October 6, 2004 at pages 6-7.

In the Advisory Action, the Examiner responded to Appellants arguments in the response to Final Office action dated January 6, 2005, as follows:

> Applicants' argument with respect to Barry is not persuasive because, although Barry lists a number of drugs that can be included in the composition, one of the compositions that is disclosed is the one where metformin is the active agent. Barry uses few examples of drugs to exemplify the compositions and those examples are examples and the prior art does not have to exemplify all the disclosed composition. It is noted that the generic claim is directed to a composition having metformin as the beneficial agent and this broad claim reads on the composition of Barry.

Advisory Action of February 22, 2005 at page 2

2. U.S. Patent No. 5,055,306 to Barry et al. does not anticipate the claims

U.S. Patent No. 5,055,306 to Barry et al. (hereinafter "the Barry reference") relates to a granular sustained-release formulation of a pharmacologically active substance presented in the form of a tablet. (See, e.g., Abstract, and col. 3, lines 36-39) The tablet purportedly includes a sufficient amount of granules to provide a predetermined dose or a number of doses of the pharmacologically active substance and effervescent or water-dispersible ingredients. (See, e.g., Abstract and col. 3, lines 39-42). Each of the granules allegedly includes a core including one or more pharmacologically active substances and preferably one or more excipients and a coating covering substantially the whole surface of the core including a water insoluble (but water swellable) acrylic polymer and a water soluble hydroxylated cellulose derivative. (See, e.g., Abstract and col. 3, lines 42-53).

Claims 1, 6, 8, 9, 12, 15, 18, 24, and 27 are directed to sustained release formulations including metfomin or a pharmaceutically acceptable salt thereof which provides "an AUC which is increased by the presence of food as compared with administration in the fasting state." Claim 31 is directed to a sustained release dosage form including metfomin or a

pharmaceutically acceptable salt thereof which "does not exhibit a decrease in the bioavailability of metformin if taken with food."

With respect to Group I, the Barry reference fails to teach a sustained release formulation comprising an active agent consisting of metformin or a pharmaceutically acceptable salt thereof which provides an AUC which is increased by the presence of food as compared with administration in the fasting state as recited in independent claims 1, 6, 8, 9, 12, 15, 18, 24, and 27. Further, the Barry reference fails to teach a sustained release formulation comprising an active agent consisting of metformin or a pharmaceutically acceptable salt thereof which does not exhibit a decrease in the bioavailability of metformin if taken with food as recited in independent claim 31.

The Barry reference further fails to teach a formulation which provides the following:

a. therapeutic plasma levels of metformin to a human patient over a 24 hour period after administration to the patient as recited in claim 1;

b. a T_{max} of the metformin which occurs at a time from about 8 hours to about 12 hours after administration to a human patient as recited in claim 6;

c. a peak of a mean plasma concentration/time curve of metformin at a time from about 4 hours to about 10 hours after administration as recited in claim 8;

d. a peak plasma concentration (C_{max}) of metformin from about 52.8% to about 75.1% of the C_{max} provided by an equivalent dose of metformin in an immediate release reference formulation as recited in claim 9;

e. a T_{max} of metformin from about 182% to about 200% of the T_{max} provided by an equivalent dose of metformin in an immediate release reference formulation as recited in claim 12;

f. a T_{max} of metformin from about 173% to about 215% of the T_{max} provided by an equivalent dose of metformin in an immediate release reference formulation as recited in claim 15;

g. a width at 50% of the height of a mean plasma concentration/time curve from about 6 hours to about 12 hours as recited in claim 18;

h. the particularly claimed dissolution profiles of metformin when tested in a United States Pharmacopeia (USP) type 2 apparatus at 75 rpm in 900 ml of simulated intestinal fluid (pH 7.5 phosphate buffer) and at 37° C as recited in claims 24 and 27; or

i. therapeutic levels of metformin attained in a human for 12 to 24 hours as recited in claim 31.

In order for the Barry reference to anticipate Group I, the Examiner has relied on inherency, stating that ". . . the function of the instant metformin formulation is inherent to the metformin formulation of the prior art . . . ."

To establish inherency, the extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 U.S.P.Q.2D (BNA) 1746, 1749 (Fed. Cir. 1991). "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.* at 1269, 20 U.S.P.Q.2D (BNA) at 1749 (quoting *In re Oelrich*, 666 F.2d 578, 581, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981). See also, *In re Rijckaert* 9 F.3d 1531, 28 U.S.P.Q.2d (BNA) 1955 (Fed. Cir. 1993) (reversed rejection, finding inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art).

In order to formulate a metformin formulation as recited in the claims of the present invention, one would have to optimize conditions, ingredients and parameters of the formulations described in the Barry reference as the Barry reference does not specifically teach how to formulate metformin utilizing their described technology. The only exemplified formulations of the Barry reference contain ibuprofen, nifedipine, naproxen, and mefenamic acid as active agents. (See, e.g,. Examples 1-8 at col. 9, line 10 to col. 16, line 58). The means to achieve the optimal conditions for formulating a metformin formulation are not disclosed explicitly nor implicitly in view of the Barry reference. Further, the mere fact that metformin can be inserted into one of the formulations of the Barry reference and may provide the functional limitations of the present claims does not rise to the level of inherent anticipation as such functional limitations must be "necessarily present" in the metformin formulations prepared in view of the Barry reference.

Further, it is respectfully submitted that based on evidence cited by the Examiner, it cannot be said that that the influence of food on the bioavailability of the metformin is a property of the metformin itself. In support of Applicants' position, a copy of the Physician's Desk Reference section on the brand name immediate release metformin product, Glucophage® (50th edition, pages 752-757) is submitted herewith as Exhibit 1. This reference was cited by the Examiner in the Office Action of October 1, 2001. Therein, at page 753, middle column, it is stated that "food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower mean peak concentration (Cmax), a 25% lower area under the plasma concentration versus time curve (AUC) and a 35 minute prolongation of time to peak plasma concentration (Tmax) following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting." (emphasis added).

It is respectfully submitted that Exhibit 1 demonstrates that the bioavailability property of the claimed sustained release dosage form when administered with food is not a property of the drug itself. In further support of this proposition, the section of the Physician's Desk Reference relating to Glucophage® was submitted by the Applicants with the Amendment of July 2, 2004

(the 52nd edition, pages 795-800 were submitted). However, it is respectfully submitted that the Examiner failed to correctly consider the description relating to Glucophage® in the Physician's Desk Reference as the Examiner continued to reject the claims as being inherent in the Barry formulations. In view of the Physician's Desk Reference it cannot be said that simply placing metfomin or a pharmaceutically acceptable salt thereof in an oral dosage form (e.g., such as those described in the Barry reference) would necessarily result in a formulation having the properties of the presently claimed invention.

The Barry reference indicates that the formulations described therein can be used with a large genus of possible active agents. This genus is listed in the Barry reference at column 7, lines 8-46. This exhaustive genus includes a multitude of compounds and the recitation of metformin (line 36) is merely a single species of the large genus described in the Barry reference.

Applicants respectfully submit that one skilled in the art would not be motivated to select the particular claimed species (i.e. metformin) from the large genus disclosed at column 7 of the Barry reference. In support of this position, it is respectfully submitted that with respect to Barry, (i) the size of the genus is not sufficiently small as to render each member of the genus inherently disclosed, (ii) the reference does not expressly teach a particular reason to select the claimed species; and (iii) there is no teaching of structural similarity in the reference. See MPEP 8th Edition, 2nd revision 2144.08 II (A)(4)(A-C). A discussion of these points follows:

(i) The size of the genus is not sufficiently small as to render each member of the genus inherently disclosed

The fact that a claimed species is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994). Some motivation to select the claimed species or subgenus must be

taught by the prior art. See e.g., *In re Deuel*, 51 F.3d at 1558-59, 34 USPQ2d at 1215. Because "anticipation is the epitome of obviousness," *Connell v. Sears, Roebuck & Co., 722 F.2d 1542, 1548 (Fed. Cir. 1983)*, it is respectfully submitted that the prior art genus of the Barry reference does not anticipate the particularly claimed species (i.e., metformin).

It is respectfully submitted that the size of the possible active agents which can be used in accordance with the Barry reference is sufficiently large as not to anticipate each and every individual species (e.g. metformin) which falls within their broad genus.

(ii) The reference does not expressly teach a particular reason to select the claimed species

If a prior art reference expressly teaches a particular reason to select the claimed species, the Examiner should point out the express disclosure which would have motivated one of ordinary skill in the art to select the claimed species. See MPEP 8th Edition, 2nd revision 2144.08 II (A)(4)(B). It is respectfully submitted that the only recitation of metformin in the Barry reference is embedded within a large genus. Accordingly, the Barry reference does not expressly teach a particular reason to select metformin from the plethora of other possible species in the genus of the reference.

(iii) There is no teaching of structural similarity in the reference

If a preferred species is structurally similar to that claimed, its disclosure may motivate one of ordinary skill in the art to choose the claimed species from the genus. See, e.g., *In re Dillon*, 919 F.2d at 693, 696, 16 USPQ2d at 1901, 1904. It is noted that the preferred active agents exemplified in the Barry reference are ibuprofen, nifedipine, naproxen and mefanamic acid in Examples 1 - 8.

It is respectively submitted that none of these active agents are similar in structure to metformin (i.e., dimethyl biguanide) and none of these agents provide similar pharmacological activity. Indeed, it is respectfully submitted that the claimed food effect of metformin sustained release formulations is not predictable based on the formulations described in the Barry reference which contain these active agents. Accordingly, as the Barry reference does not teach any preferred species which have structural similarity to metformin, there is no motivation therein to one skilled in the art to select metformin from the large genus.

Further, any teaching or suggestion in the reference of a preferred species that is significantly different in structure from the claimed species weigh against selecting the later selected species. See, e.g., *In re Baird*, 16 F.3d 382-83, 29 USPQ2d 1552 (Fed. Cir. 1994). Accordingly, the examples of the Barry reference directed to compounds that are not structurally similar to metformin is further evidence that one skilled in the art would not be motivated to select metformin from the genus described therein.

Accordingly, Appellants believe that the independent claims of Group I are patentable over the Barry reference and respectfully request that this rejection be reversed. As claims 4, 10, 11, 13, 14, 16, 17, 25, 26, 28, and 29 depend from the independent claims of Group I, and include all the limitations of the independent claims from which they depend, Appellants submit that the rejection of these dependent claims should also be reversed.

B. 35 U.S.C. §103 Rejection of Group II (Claims 33 and 35-39) Based Upon U.S. Patent No. 5,055,306 to Barry et al.

Independent claim 33 is directed to a method of treating a human diabetic patient with an oral solid dosage form of metformin, comprising: swallowing on a once a day basis in the presence of food an intact controlled release oral dosage form containing (i) an active agent consisting of an effective amount of metformin or a pharmaceutically acceptable salt thereof and one or more materials controlling the release of metformin from the dosage form such that

therapeutic levels of the metformin are attained in the human for 12 to 24 hours and a decrease in the bioavailability of metformin is not exhibited.

Independent claim 35 is directed to a method of treating diabetes in humans, comprising: swallowing on a once a day basis in the presence of food an intact controlled release solid oral dosage form containing (i) an active agent consisting of a therapeutically effective metformin or a pharmaceutically acceptable salt thereof, and (ii) a sustained release material, such that therapeutic plasma levels of metformin are attained in said human over the dosing interval and (i) a decrease in the bioavailability of metformin is not exhibited relative to administration of the dosage form in the fasting state; or (ii) an increase in the bioavailability of metformin is exhibited relative to administration of the dosage form in the fasting state.

1. The Examiner's rejection

The second issue presented is whether claims 33 and 35-39 are unpatentable under 35 U.S.C. §103(a) as being obvious over the Barry reference. In response to the Final Office Action, independent claims 33 and 35 were amended to recite "...swallowing an intact dosage form..." For purposes of the appeal, the amendment to the claims was entered by the Examiner as indicated in the Advisory Action of February 22, 2004, paragraph 7.

In the final Office Action, the Examiner stated that "[t]his obviousness rejection is based on the premise that it would be within the purview of the person of ordinary skill or the skilled artisan to ascertain the ideal times for administering the formulation, that is with food or in fasting state and the rejection is not anticipatory."

The Examiner further stated that "the burden is on applicants to provide a proof to demonstrate the difference between the instant metformin and the metformin of the prior art or to show that the metformin of the prior art would not possess the inherent recited characteristics/property/function."

As noted above, in the Advisory Action, the Examiner responded to Appellants arguments in the response to Final Office action dated October 6, 2004, as follows:

> Applicants' argument with respect to Barry is not persuasive because, although Barry lists a number of drugs that can be included in the composition, one of the compositions that is disclosed is the one where metformin is the active agent. Barry uses few examples of drugs to exemplify the compositions and those examples are examples and the prior art does not have to exemplify all the disclosed composition. It is noted that the generic claim is directed to a composition having metformin as the beneficial agent and this broad claim reads on the composition of Barry.

Advisory Action of Feb. 22, 2004 at page 2.

In the Advisory Action, the Examiner did not consider the limitations to claims 33 and 35 directed to "...swallowing an intact dosage form..."

2. U.S. Patent No. 5,055,306 to Barry et al. does not render the claims obvious

Independent claim 33 recites a method of treating a human diabetic patient with an oral solid dosage form of metformin, comprising **swallowing** on a once a day basis in the presence of food an **intact** controlled release dosage form . . . ." (emphasis added). Similarly, independent claim 35 recites a method of treating diabetes in humans, comprising **swallowing** on a once a day basis in the presence of food an **intact** controlled release dosage form . . . ." (emphasis added).

The Barry reference is directed to effervescent or water dispersible dosage forms which are administered by disintegrating the dosage form in an aqueous liquid prior to administration (See, e.g., col. 5, lines 43-55 of Barry) or by sucking and swallowing material released from the

tablet (See, e.g., col. 10, lines 46-54 of Barry). In contrast, in the claimed methods of treatment of claims 33 and 35, the controlled release metformin dosage forms are **swallowed intact**.

The Barry reference does not teach or suggest "...**swallowing** an **intact** dosage form..." as recited in independent claims 33 and 35, nor would one of ordinary skill in the art be motivated to do so in view of the Barry reference as the dosage forms of the Barry reference are not meant to be swallowed intact.

In addition, the Barry reference actually **teaches away** from the presently claimed invention, as the very purpose of the Barry reference is counter-intuitive to the Appellants presently claimed invention of claims 33 and 35. The formulations of the Barry reference are described as "presented in the form of tablets which disintegrate into sustained-release granules upon coming into contact with an aqueous liquid." (See *Barry et al.* at Col. 4, lines 6-9). This purportedly overcomes the difficulties associated with conventional sustained-release formulations, enabling large dosages in sustained-release form to be more easily administered to, and swallowed by, the patient. (See *id.* at Col. 2, lines 61-68).

In view of the Barry reference, one of ordinary skill in the art would not be motivated to treat a human patient comprising swallowing an intact controlled release dosage form as recited in claims 33 and 35 of the present invention, as the tablets of the Barry reference are formulated to disperse or effervesce in the mouth of the patient upon administration.

Accordingly, Appellants believe that the independent claims of Group II are patentable over the Barry reference and respectfully request that this rejection be reversed. As claims 36-37 and 39 depend from the independent claims of Group II and include all the limitations of independent claims from which they depend, Appellants submit that the rejection of these dependent claims should also be reversed.

C. Conclusion

Appellants claimed formulations and methods are substantially different from the formulations and methods described in the Barry reference. The claimed formulations and methods have limitations which are not taught nor suggested by the Barry reference. Appellants believe that for the foregoing reasons the final rejections of claims should be reversed.

Prompt consideration of the arguments presented herein and reversal of the final rejections is earnestly solicited.

Respectfully submitted,
DAVIDSON, DAVDISON & KAPPEL, LLC

By:_____
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IX. APPENDIX

Listing of Claims:

Claim 1. (Previously Presented) A sustained release pharmaceutical formulation comprising (i)an active agent consisting of metformin or a pharmaceutically acceptable salt thereof, and (ii) a sustained release material, wherein said formulation provides therapeutic plasma levels of said metformin to a human patient over a 24 hour period after administration to said patient; and said formulation providing an AUC which is increased by the presence of food as compared with administration in the fasting state.

Claims 2-3. (Cancelled)

Claim 4. (Previously Presented) The sustained release pharmaceutical formulation of claim 1 wherein said formulation provides a time to peak plasma concentration (T_{max}) of the metformin which occurs at a time from about 8 hours to about 12 hours after administration to said human patient.

Claim 5. (Cancelled)

Claim 6. (Previously Presented) A sustained release pharmaceutical formulation comprising (i)an active agent consisting of a dose of metformin or a pharmaceutically acceptable salt thereof suitable for once daily dosing, and (ii) a sustained release material, said formulation providing a T_{max} of the metformin which occurs at a time from about 8 hours to about 12 hours after administration to a human patient; and said formulation providing an AUC which is increased by the presence of food as compared with administration in the fasting state.

Claim 7. (Cancelled)

Claim 8. (Previously Presented) A sustained release pharmaceutical formulation comprising (i)an active agent consisting of metformin or a pharmaceutically acceptable salt thereof, and (ii) a sustained release material, said formulation suitable for once daily dosing and providing a peak of a mean plasma concentration/time curve of metformin at a time from about 4 hours to about 10 hours after administration; and said formulation providing an AUC which is increased by the presence of food as compared with administration in the fasting state.

Claim 9. (Previously Presented) A sustained release pharmaceutical formulation comprising (i)an active agent consisting of a dose of metformin or a pharmaceutically acceptable salt thereof suitable for once daily dosing, and (ii) a sustained release material, said formulation when administered with or after a meal to a human patient, providing a peak plasma concentration (C_{max}) of metformin from about 52.8% to about 75.1% of the C_{max} provided by an equivalent dose of metformin in an immediate release reference formulation; and said formulation providing an AUC which is increased by the presence of food as compared with administration in the fasting state.

Claim 10. (Original) The sustained release pharmaceutical formulation of claim 9 wherein said formulation provides a T_{max} of the metformin which occurs at a time from about 8 hours to about 12 hours after administration to said human patient.

Claim 11. (Original) The sustained release pharmaceutical formulation of claim 9 wherein the bioavailability of the drug is increased by the presence of food.

Claim 12. (Previously Presented) A sustained release pharmaceutical formulation comprising (i) an active agent consisting of a dose of metformin or a pharmaceutically acceptable salt thereof suitable for once daily dosing, and (ii) a sustained release material, said formulation when administered with or after a meal to a human patient, providing a T_{max} of metformin from about 182% to about 200% of the T_{max} provided by an equivalent dose of metformin in an

immediate release reference formulation; and said formulation providing an AUC which is increased by the presence of food as compared with administration in the fasting state.

Claim 13. (Original) The sustained release pharmaceutical formulation of claim 12 wherein said formulation provides a T_{max} of the metformin which occurs at a time from about 8 hours to about 12 hours after administration to said human patient.

Claim 14. (Original) The sustained release pharmaceutical formulation of claim 12 wherein the bioavailability of the metformin is increased by the presence of food.

Claim 15. (Previously Presented) A sustained release pharmaceutical formulation comprising (i) an active agent consisting of a dose of metformin or a pharmaceutically acceptable salt thereof suitable for once daily dosing, and (ii) a sustained release material, said formulation when administered in the fasted state to a human patient, providing a T_{max} of metformin from about 173% to about 215% of the T_{max} provided by an equivalent dose of metformin in an immediate release reference formulation; and said formulation providing an AUC which is increased by the presence of food as compared with administration in the fasting state.

Claim 16. (Original) The sustained release pharmaceutical formulation of claim 15 wherein said formulation provides a T_{max} of the metformin which occurs at a time from about 8 hours to about 12 hours after administration to a human patient.

Claim 17. (Original) The sustained release pharmaceutical formulation of claim 15 wherein the bioavailability of the metformin is increased by the presence of food.

Claim 18. (Previously Presented) A sustained release pharmaceutical formulation comprising (i) an active agent consisting of a dose of metformin or a pharmaceutically acceptable salt thereof suitable for once daily dosing, and (ii) a sustained release material, said formulation upon administration to a human patient, providing a width at 50% of the height of a mean plasma

concentration/time curve from about 6 hours to about 12 hours; and said formulation providing an AUC which is increased by the presence of food as compared with administration in the fasting state.

Claim 19. (Original) The sustained release pharmaceutical formulation of claim 18 wherein said formulation provides a T_{max} of the metformin which occurs at a time from about 8 hours to about 12 hours after administration.

Claims 20. (Original) The sustained release pharmaceutical formulation of claim 18 wherein the bioavailability of the metformin is increased by the presence of food.

Claims 21-23. (Cancelled)

Claim 24. (Previously Presented) A sustained release pharmaceutical formulation comprising (i) an active agent consisting of a dose of metformin or a pharmaceutically acceptable salt thereof, and (ii) a sustained release material, that exhibits the following dissolution profile when tested in a United States Pharmacopeia (USP) type 2 apparatus at 75 rpm in 900 ml of simulated intestinal fluid (pH 7.5 phosphate buffer) and at 37° C.:
after 2 hours 0-25% of the metformin or salt thereof is released;
after 4 hours 10-45% of the metformin or salt thereof is released;
after 8 hours 30-90% of the metformin or salt thereof is released;
after 12 hours not less than 50% of the metformin or salt thereof is released;
after 16 hours not less than 60% of the metformin or salt thereof is released;
and after 20 hours not less than 70% of the metformin or salt thereof is released; and wherein after administration to a human patient, said formulation providing an AUC which is increased by the presence of food as compared with administration in the fasting state.

Claim 25. (Previously Presented) The sustained release pharmaceutical formulation of claim 24 wherein after administration to the human patient, said formulation provides a biovailability of metformin which is increased by the presence of food.

Claim 26. (Original) The sustained release pharmaceutical formulation of claim 24 wherein after administration to a human patient, said formulation provides a T_{max} of metformin which occurs at a time from about 8 hours to about 12 hours after said administration.

Claim 27. (Previously Presented) A sustained release pharmaceutical formulation comprising (i) an active agent consisting of a dose of metformin or a pharmaceutically acceptable salt thereof and (ii) a sustained release material, that exhibits the following dissolution profile when tested in a USP type 2 apparatus at 75 rpm in 900 ml of simulated intestinal fluid (pH 7.5 phosphate buffer) and at 37° C.:
after 2 hours 0-15% of the metformin or salt thereof is released;
after 4 hours 20-40% of the metformin or salt thereof is released;
after 8 hours 45-90% of the metformin or salt thereof is released;
after 12 hours not less than 60% of the metformin or salt thereof is released;
after 16 hours not less than 70% of the metformin or salt thereof is released;
and after 20 hours not less than 80% of the metformin or salt thereof is released; and wherein after administration to a human patient, said formulation providing an AUC which is increased by the presence of food as compared with administration in the fasting state.

Claim 28. (Previously Presented) The sustained release pharmaceutical formulation of claim 27 wherein after administration to the human patient, said formulation provides a bioavailability of metformin which is increased by the presence of food.

Claim 29. (Original) The sustained release pharmaceutical formulation of claim 27 wherein after administration to a human patient, said formulation provides a T_{max} of metformin which occurs at a time from about 8 hours to about 12 hours after said administration.

Claim 30. (Previously Presented) The sustained release pharmaceutical formulation of claim 1 wherein said metformin or pharmaceutically acceptable salt thereof is metformin hydrochloride.

Claim 31. (Previously Presented) A sustained release once a day oral solid dosage form of metformin, comprising (i) an active agent consisting of an effective amount of metformin or a pharmaceutically acceptable salt thereof and one or more materials controlling the release of metformin from the dosage form such that said dosage form, when orally administered on a once a day basis to a human in the presence of food, therapeutic levels of said metformin are attained in said human for 12 to 24 hours, and said dosage form does not exhibit a decrease in the bioavailability of metformin if taken with food.

Claim 32. (Previously Presented) The sustained release dosage form of claim 31, which provides an increase in the bioavailability of said metformin if taken with food.

Claim 33. (Previously Presented) A method of treating a human diabetic patient with an oral solid dosage form of metformin, comprising:

swallowing on a once a day basis in the presence of food an intact controlled release oral dosage form containing (i) an active agent consisting of an effective amount of metformin or a pharmaceutically acceptable salt thereof and one or more materials controlling the release of metformin from the dosage form such that therapeutic levels of said metformin are attained in said human for 12 to 24 hours and a decrease in the bioavailability of metformin is not exhibited.

Claim 34. (Cancelled)

Claim 35. (Previously Presented) A method of treating diabetes in humans, comprising:

swallowing on a once a day basis in the presence of food an intact controlled release solid oral dosage form containing (i) an active agent consisting of a therapeutically effective metformin or a pharmaceutically acceptable salt thereof, and (ii) a sustained release material,

such that therapeutic plasma levels of metformin are attained in said human over the dosing interval and (i) a decrease in the bioavailability of metformin is not exhibited relative to administration of the dosage form in the fasting state; or (ii) an increase in the bioavailability of metformin is exhibited relative to administration of the dosage form in the fasting state.

Claim 36. (Previously Presented) The method of claim 35, further comprising administering said dosage form with or shortly after an evening meal.

Claim 37. (Previously Presented) The method of claim 35, wherein an increase in the AUC is exhibited as compared with administration in the fasting state.

Claim 38. (Previously Presented) The sustained release dosage form of claim 31, which provides an AUC which is increased by the presence of food as compared with administration in the fasting state.

Claim 39. (Previously Presented) The method of claim 33, wherein an increase in the AUC is exhibited as compared with administration in the fasting state.